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(54) Title: **PROCESS FOR RESOLUTION OF TAMSULOSIN**

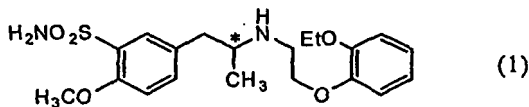
(57) Abstract: Optically impure tamsulosin including racemic tamsulosin can be resolved into optically pure (R)- or (S)-tamsulosin by the use of diastereomeric sulfonate salts of tamsulosin in a fractional crystallization technique.

PROCESS FOR RESOLUTION OF TAMSULOSIN

BACKGROUND OF THE INVENTION

The present invention relates to a process for the resolution of (R,S)-5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzene-sulfonamide, also known as tamsulosin, into optically enriched and/or optically pure enantiomers and to compounds and compositions useful therein.

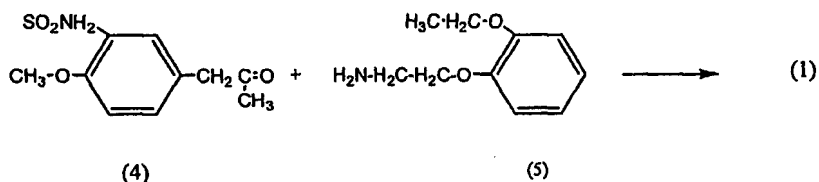
The compound 5-[2-[[2-(2-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide of the formula (1)



is a commercially marketed pharmaceutically active substance useful for treatment of cardiac insufficiencies and benign prostatic hyperplasia. It is disclosed in EP34432 and US 4731478. The molecule, which will be further denoted as "tamsulosin," has one asymmetric carbon (indicated by an asterisk in the above formula (1)), thus allowing for the existence of two enantiomers, conventionally denoted as (R)- or (S)-enantiomers. Both the free base and its acid addition salts thereof may comprise either one or both of the two enantiomers. The single enantiomers have distinctive optical activity in polarized light and they also differ in their pharmacologic activities. The

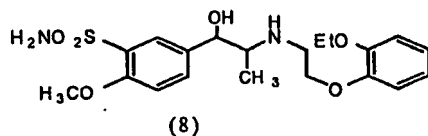
commercially marketed product is the hydrochloride salt of the (R)-enantiomer of tamsulosin which is levorotary or (R)(-) tamsulosin hydrochloride.

EP34432/ US 4731478 discloses, *inter alia*, two general processes that may provide tamsulosin. One general process (hereinafter "process A") comprises a reductive amination of a benzylmethylketone compound with a substituted phenoxyethylamine. To make tamsulosin, the corresponding species would be represented by formulae (4) and (5), respectively.



However, neither these compounds nor the details of an actual production process leading to tamsulosin using this process is set forth. Instead, process A was exemplified only for alkylsulfonamide derivatives. Accordingly, the compounds (4) and (5) were also not prepared as chemical entities. Further, the exemplified products of process A, see examples 4 and 5, were crystallized as the hydrochloride salt of the racemate. If process A is applied for the synthesis of tamsulosin, the result would allow for producing a racemic tamsulosin isolated in the form of a hydrochloride salt.

The second process (hereinafter "process B") generically teaches conversion of a hydroxylated analogue into the desired sulfonamide via a chloro-analogue. For making tamsulosin, the hydroxy analogue would be a compound of formula (8).



It was disclosed therein that the starting hydroxy-analogues may be prepared according to the methods of GB 2006772, which correspond to DE 2843016 and US 4217305. However, none of these documents specifically show the formation of this hydroxy-tamsulosin intermediate compound. Further, it appears in both US 4731478 and GB 2006772 that only racemic tamsulosin and racemic hydroxy-tamsulosin, respectively, would be prepared by this general reaction scheme, and not the pure enantiomer. Note that tamsulosin was not prepared by this process in US 4731478. It can be derived that condensation of the compound (5) with a suitable reaction partner (geminal halohydrin or oxiran), according to GB 2006772, would produce racemic hydroxy-tamsulosin that would then be correspondingly converted to racemic tamsulosin.

A method of resolution of racemic tamsulosin into optical isomers was not disclosed in above prior art documents. The only process disclosed in US 4731478 that obtains optically pure enantiomeric forms is not in accord with process A or process B, but instead comprises reacting optically pure 5-((2-amino-2-methyl)ethyl)-2-methoxybenzenesulfonamide with 2-(o-ethoxyphenoxy)ethyl bromide to form the corresponding (R)- or (S)-tamsulosin. See Examples 33(a) and 33(b). Known processes for providing the optically pure amine, e.g. processes disclosed in JP 58-

18353, EP257787, JP 02-679248, are lengthy and complicated. If the starting amine does not have a desired optical purity, the produced tamsulosin would accordingly be prepared in an optically impure form (in a mixture of enantiomers). No method is known how to purify such an optically impure product.

It would be desirable to have a method to resolve optically impure tamsulosin, including racemic tamsulosin. Specifically, it is desirable to provide for a process for the resolution of a racemic tamsulosin or a mixture of tamsulosin enantiomers, which could manufacture the desired enantiomer, particularly the (R) enantiomer, in a desired purity.

SUMMARY OF THE INVENTION

The present invention relates to the resolution of tamsulosin enantiomers by the use of diastereomeric salts thereof, especially camphor sulfonate salts, by crystallization and to the compounds and compositions used therein and produced thereby. In particular, one aspect of the invention relates to a process comprising preferentially precipitating one diastereomeric sulfonate salt of tamsulosin from a solution containing a pair of diastereomeric sulfonate salts of tamsulosin to form diastereomeric enriched precipitate and diastereomeric enriched solute. The enriched tamsulosin free base enantiomer can be liberated from either the enriched precipitate or the enriched solute. The precipitation can be repeated with or without first liberating the free base.

Similarly, another aspect of the present invention relates to a method of separation of enantiomers of tamsulosin by fractional crystallization comprising using a chiral camphor sulfonic acid in said crystallization.

A further aspect of the invention relates to a compound selected from the group consisting of (R)-tamsulosin-(+)-camphor-10-sulfonate, (S)-tamsulosin-(+)-camphor-10-sulfonate, (R)-tamsulosin-(-)-camphor-10-sulfonate, and (S)-tamsulosin-(-)-camphor-10-sulfonate. For clarity, while these salts are diastereomers, the (R) and (S) denotation indicates the stereo configuration of the tamsulosin moiety and (+) and (-) denotation indicates the optical activity of the acid from which the diastereomeric salt was formed. These diastereomers are particularly useful in preferential precipitation according to the present invention.

Another aspect of the present invention relates to a composition comprising (R) and (S) tamsulosin or the salts thereof, wherein one of said (R) or (S) forms exceeds the amount of the other within the range of 60:40 to 95:5, preferably 65:35 to 95:5 parts by weight. Such compositions can be formed by the process of the present invention and/or are useful as substrates in the resolution process of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the resolution of tamsulosin. The process of resolving tamsulosin comprises preferentially precipitating one diastereomeric sulfonate salt of tamsulosin from a solution that contains a pair of diastereomeric

sulfonate salts of tamsulosin to form a precipitate that is enriched with one diastereomer and a solute (or remaining mother liquor) that is enriched with the other diastereomer. The invention is based on the discovery that diastereomeric sulfonate salts of tamsulosin are easily separated by crystallization. Such a process is sometimes referred to as fractional crystallization.

The solution that contains the diastereomers can be formed in a variety of ways. For example, tamsulosin substrate can be reacted in a solvent with a sulfonic chiral acid to form a pair of diastereomers in solution. Alternatively, a solid mixture of diastereomers such as a precipitate or a diastereomeric enriched precipitate can be dissolved in a solvent to form the solution. Thus, regardless of how the solution containing diastereomeric sulfonic acid salts of tamsulosin is formed, any preferential precipitation of one of the diastereomers from such a solution is contemplated as being within the scope of the present invention.

The substrate for the process of the invention (= tamsulosin substrate) is a mixture of tamsulosin enantiomers. The mixture of (R) and (S) enantiomers can be equimolar (50:50) as in racemic tamsulosin or a racemic mixture of tamsulosin enantiomers, or unequal. In some embodiments the amount of one enantiomer can be significantly greater than the amount of the other enantiomer, especially if the process is being applied to a tamsulosin substrate already partially resolved into enantiomers or to a substrate made by an optically specific method that has insufficient optical purity.

The applicability of the resolution process of the invention is not limited to racemic tamsulosin free base in solid state. In the substrate for resolution, tamsulosin may be present either in a form of free base or as an acid addition salt other than a salt with a chiral acid. In all these forms, tamsulosin may be applied in an isolated state, such as a crystalline or non-crystalline solid, a semisolid or liquid, or in a solution or as a product of a chemical reaction, i.e. as a raw product or reaction mixture obtained in the last step of the manufacturing process leading to it. It may be used either crude or purified by any suitable method, in any solvated or hydrated form.

The most advantageous tamsulosin substrate for the process of optical resolution is optically impure or racemic tamsulosin free base. The free base may be prepared by various processes listed below. Moreover, a novel, suitable procedure for isolating tamsulosin free base in solid state is set forth hereinafter. The solid state, particularly crystalline, form of tamsulosin free base is a preferred substrate. Additionally, it is preferred that the tamsulosin free base be in pure form, such as 80% or more pure, preferably 90% or more pure, and even 95% or more pure from non-tamsulosin impurities.

The racemic or otherwise optically impure tamsulosin substrate is converted into the diastereomeric salt pair by contacting the substrate in a suitable solvent with a suitable optically active (i.e., chiral) sulfonic acid. The chiral sulfonic acids useful within the present invention are preferably monovalent organic sulfonic acids having pKa value lower than about 3.5. Preferred chiral acids are camphor sulfonic acids including lower alkyl and/or halo derivatives thereof. Specifically preferred acids are

(-)-camphor-10-sulfonic acid and (+)-camphor-10-sulfonic acid. These acids are commercially available and can be made by methods well known in the art.

The amount of the chiral acid used in forming the diastereomeric pair is typically within the range of 0.5 - 2 moles per 1 mole of tamsulosin and is preferably essentially equimolar.

The solvent is selected so as to facilitate the salt reaction and preferably to allow subsequent separation of the resulting diastereomers by fractional crystallization. In the process, a mixture of tamsulosin substrate (free base or salt) with a solvent may be contacted with a solid chiral acid, or a mixture of chiral acid with a solvent may be contacted with solid tamsulosin, or both partners may be combined with a solvent prior to being contacted together. The contact may be made using a single solvent or a mixture of solvents. Normally the substrate and the acid are dissolved in the solvent, even if they started as a solid at the beginning of the contact, in order to facilitate an efficient salt reaction. Suitable solvents include lower alcohols especially methanol and ethanol, acetone, dioxane, ethyl acetate, mixtures thereof, and mixtures of one or more of these solvents with water. Preferred solvents are methanol and methanol-water mixtures.

The temperature of contact is from ambient to the boiling point of the solvent system, the later being preferred. It is not required that a complete solution is formed in this step, though it is preferred.

The salt reaction forms a pair of diastereomers: one diastereomer resulting from the reaction of (R)-tamsulosin with the chiral sulfonic acid and another resulting

from the reaction of the (S)-tamsulosin with the chiral sulfonic acid. One of the diastereomers is preferentially precipitated from the solvent. The precipitation is "preferential" in that the conditions used allow for one of the diastereomers to be precipitated to a greater extent than the other. The precipitation of the solid phase may be spontaneous, or may be induced by changing the conditions of the solution, e.g. by cooling the mixture after contact, adding a contra-solvent, removal of a part of the solvent or by combination of these techniques. As used herein "induced" includes partially induced such as where some precipitation occurs spontaneously and more precipitation is achieved by an inducement technique as well as precipitation achieved by only an inducement technique. The precipitation, whether spontaneous or induced, may also be facilitated by the presence of or inoculation with a seeding crystal of the desired salt.

The obtained solid salt is substantially enriched by one enantiomer of tamsulosin, advantageously by the (R)-tamsulosin. As used herein "enrichment" means that the product contains more of one of the (R)- or (S)- tamsulosin or tamsulosin diastereomer than the starting substrate or composition. For example, if the starting tamsulosin contained a 50:50 mixture of (R) and (S) enantiomers, then a precipitation of a salt having an (S):(R) tamsulosin ratio of 30:70 would be a diastereomeric enriched precipitate because the diastereomer having (or derived from) the (R)-tamsulosin has been increased relative to the amount in the initial solution. Similarly, the mother liquor is likewise enriched by the other diastereomeric salt formed from the second enantiomer, e.g. (S)-tamsulosin, and thus is a diastereomeric

enriched solute. The ratio of diastereomers in the initial solution is not limited to racemic mixtures and includes solutions where one diastereomer is contained in a greater amount than the other. Preferred solutions contain diastereomers of the (R):(S)-tamsulosin in a ratio from 65:35 to 95:5 or more and typically include solutions having a ratio within the range of 70:30 to 95:5, more typically 75:25 to 85:15. In these later cases, enrichment occurs so long as the precipitate (and solute) has a different ratio of one diastereomer to the other than in the solution. For example, a solute having a ratio of diastereomeric (R):(S) tamsulosin of 87:13 is an enriched solute from a solution that contained diastereomeric (R):(S) tamsulosin of 65:35. The degree of enrichment (optical yield) is preferably at least 50%, typically at least 75%, more typically at least 80% and preferably is at least 90%.

In a preferred variant, the diastereomeric salt of the desired (R) isomer of tamsulosin with a chiral acid is less soluble than that of the diastereomer of the (S) isomer and thus the (R) form preferentially precipitates out of the solution. The precipitate may be separated from the reaction mixture by ordinary methods such as by filtration or centrifugation.

In a second variant, the salt of the desired (R)-tamsulosin isomer with a chiral acid is more soluble than that of the (S) isomer and it remains in the solution after separation of the solid. Then, the mother liquor contains the desired enantiomer of tamsulosin and may be elaborated by various ways. For instance, the solvent may be evaporated or a contrasolvent may be added to obtain the desired salt in solid state. Advantageously, the salt is not isolated in a solid state and the obtained solution is

used as such in the next step of liberation of (R)-tamsulosin from the salt. Optical yields of this variant are similar to those as above.

An example of an advantageous embodiment of the optical resolution process of the invention, substantially racemic tamsulosin reacts with (-)-camphor-10-sulfonic acid in a methanol whereby (R)-tamsulosin (-)-camphor-10-sulfonate separates out from the solution as a solid, while the salt of the (S) enantiomer remains in the solution. The (R) salt may be separated from the reaction mixture after precipitation by ordinary methods e.g. by filtration or centrifugation. The diastereomeric salt may be also isolated in solvated or hydrated form.

Alternatively, the salt of the desired (R) isomer can be more soluble than the (S) isomer in which case the diastereomer containing (S)-tamsulosin is preferentially precipitated and the diastereomer containing (R)-tamsulosin preferentially remains in the solution. This case occurs, e.g., in preparing salts with (+)-camphor-10-sulfonic acid. The (R) diastereomer of tamsulosin (+)-camphor-10-sulfonate remaining in the solution may be elaborated by evaporation to obtain the salt in solid state or may be used in any subsequent process steps as it is.

Thus, because both the precipitated and the remaining dissolved diastereomers are enriched, either the precipitated or the remaining dissolved form can be used. The optical yield can be increased by re-precipitation of the diastereomeric enriched precipitate from a suitable solvent (a re-precipitation solvent); advantageously, the same kind of solvent as was used in the solution for the initial precipitation. The re-precipitation forms a further enriched precipitate and an enriched re-precipitation

solute. The further enriched precipitate can be isolated by any known means as described above. Conversely, the re-precipitation solute is advantageously combined with the initial solute to enhance the yield of the non-precipitating diastereomer.

It is preferred, however, that the (R)-tamsulosin containing diastereomer be precipitated from the solvent. The precipitated enriched salt may be advantageously isolated from the reaction mixture and optionally re-precipitated or (re)crystallised before being used in any subsequent process step. If, however, the (S)-tamsulosin containing diastereomer preferentially precipitates, then the solute is accordingly enriched by the (R)-tamsulosin containing diastereomer. It is advantageous to combine such enriched solute with the liquid phase of the original reaction mixture or solution to increase the yield of the desired (R)-tamsulosin in subsequent reaction step.

Preferred diastereomeric pairs include (R)- and (S)-tamsulosin (-)-camphor-10-sulfonates and (R)- and (S)-tamsulosin (+)-camphor-10-sulfonates. Each one of these diastereomers is a specific aspect of the present invention. The (R)-tamsulosin containing diastereomer is particularly preferred. Moreover, the optical purity of such compounds is desired to be high, for example at least 75% of the salt material having the (R) tamsulosin configuration, more preferably at 80 %, more preferably at least 90%, still more preferably at least 95%, and still more preferably at least 99% including 99.5% or greater.

(R)-tamsulosin(-)-camphor-10-sulfonate can be isolated in a solid state as a crystalline substance. Highly pure forms solid state forms thereof preferably have at least one of the following characteristics: IR absorbance peaks of 1740, 1505, 1161 and

1044 cm^{-1} (in KBr), a melting range of 208-211°C, or an optical rotation of about -17.2° ($c=0.5$ in methanol). The IR spectrum of the compound is exemplified in Fig. 1. Of course, the (R)-tamsulosin(-)-camphor-10-sulfonate can and will have additional IR absorbance peaks as well as other physical properties not mentioned above.

The salt substantially enriched by the desired enantiomer of tamsulosin, either the precipitate or the solute, is elaborated in the next step to liberate the so enriched tamsulosin from the salt form. The liberation step essentially comprises treatment of the salt (in solid, suspended or dissolved state) with an organic or inorganic base. The base should be stronger than the basicity of tamsulosin.

The organic or inorganic base liberates both the tamsulosin and the used chiral acid from their mutual salt form and forms a new salt with such acid, while tamsulosin substantially enriched by the desired enantiomer is obtained as a free base.

The liberation step is advantageously performed in a solvent which at least partially dissolves the used salt and base. Generally, the liberation of the desired enantiomer of tamsulosin from the enriched salt proceeds by contacting the salt with an equivalent of a suitable base, e.g., metal hydroxides, in a proper solvent, advantageously in water. The so formed free base of the enriched tamsulosin is isolated by ordinary methods. If water has been employed as a solvent for neutralization, the tamsulosin base precipitates as a solid and is isolated by filtration or centrifugation.

Alternatively, the salt is contacted with water, then acidified with a stronger acid, e.g. with hydrochloric acid, and the liberated resolution agent is removed by

extraction with an organic solvent e.g. with ethylacetate. Tamsulosin remains in the aqueous layer and is precipitated therefrom as a free base by alkalization, e.g. with sodium hydroxide solution.

Any conventional method applicable to decomposition of tamsulosin salt and liberation of tamsulosin base may be employed. Advantageously, such methods are preferred that allow the isolation of, and, if advantageous, the reprocessing of the resolution agent. The resulting liberated free base preferably contains an enrichment of the (R)-tamsulosin or a salt thereof. Preferred tamsulosin compositions contain the (R):(S)-tamsulosin in a ratio from 65:35 to 99.9: to 0.1. Typical compositions containing enriched but not optically pure (R) form include an (R):(S) ratio of 65:35 to 95:5 or more and typically include solutions having a ratio within the range of 70:30 to 95:5, more typically 75:25 to 85:15.

In a preferred aspect, the obtained product comprises substantially the (R)-isomer of tamsulosin. The formed free base of tamsulosin, especially the enriched (R) enantiomer, may be further converted into an acid addition salt with a suitable acid, particularly with a pharmaceutically acceptable acid, by methods known per se. Examples of such salts are the hydrochloride, hydrobromide, acetate, fumarate, maleate, citrate or methane sulfonate.

If the optical purity of the obtained tamsulosin product is not sufficient, the resolution may be enhanced by repeating the process. The same or another chiral sulfonic acid may be employed in the repeated process. Accordingly, a second pair of diastereomeric tamsulosin can be the same or different as the first pair. In one

embodiment, the second pair is different than the first such as by using a chiral sulfonic acid that is different in rotation from the first acid. In certain embodiments, it is advantageous that the first precipitation preferentially precipitates the diastereomer containing the (S)-tamsulosin and the second precipitation from a second solvent preferentially precipitates the (R)-tamsulosin containing diastereomer. In this embodiment, the enriched solute from the first precipitation is used either with or without liberation of the tamsulosin free base to make the solution for the second precipitation.

An example is as follows. Racemic tamsulosin is treated with (+) camphor-10-sulphonic acid whereby most of the undesired (S) enantiomer is separated as a solid salt with said acid and the salt with the desired (R) enantiomer remains in the liquid phase. Therefrom, the tamsulosin free base is liberated in solid state by an action of a base and is separated from the mother liquor (solute). The solid enriched by the (R) enantiomer of tamsulosin base is then treated with (-)-camphor-10-sulphonic acid to form a pair of diastereomers. The desired salt precipitates from the solution and is isolated, converted to free base and, if necessary, recrystallized. The essentially pure (R) isomer of tamsulosin is then converted into a pharmaceutically acceptable salt, e.g. to a hydrochloride salt.

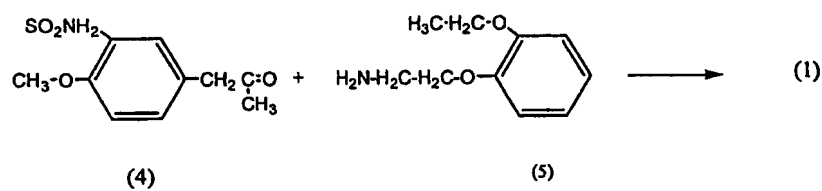
Similarly, the process may be applied to tamsulosin products from a synthesis or recovered from mother liquors, which are insufficiently pure (R)-tamsulosin. In either case, the product containing the (R)-tamsulosin is accordingly treated with a suitable chiral organic sulfonic acid in a suitable solvent, fractionally crystallized to

obtain an enriched diastereomer, and the optically purer product is liberated from the desired fraction of the salt. The tamsulosin free base can be converted to a pharmaceutically acceptable salt as mentioned above.

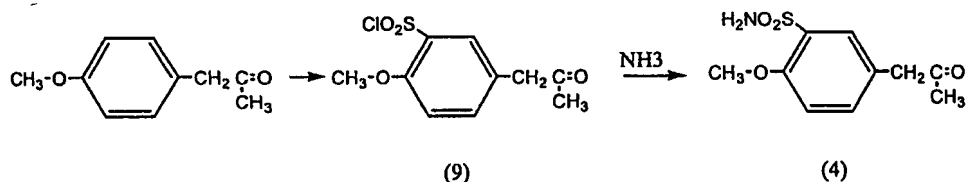
The compositions, in summary, that comprise (R)- and (S)-tamsulosin, or salts thereof, wherein one of the (R) or (S) forms is in excess to the other, can be used as starting materials or substrates for the various processes of the present invention, or can be formed as products of the processes of the present invention. Generally, the ratio of the excessive or majority form to the minority form is within the range of 60:40 to 95:5, and typically 65:35 to 95:5, parts by weight. The tamsulosin can be a salt such as a diastereomeric salt, especially camphor-10-sulfonic acid salts, or a simple pharmaceutically acceptable salt such as a hydrochloride salt. Alternatively, the tamsulosin can be a free base. The composition can be in a solid form, especially a precipitate optionally isolated and dried from the solvent or mother liquor, or in a solution form such as the solute. In one embodiment, the amount of (R)-tamsulosin is the majority and the (S)-tamsulosin is the minority. Preferred ranges for the relative amounts of (R):(S) in this embodiment are 61:39 to 87:13, more typically 65:35 to 85:15, and still more typically 75:25 to 85:15, parts by weight.

The typical starting tamsulosin substrate, namely racemic tamsulosin free base in solid state, is not formed in the prior art per se. Three preferred processes for obtaining a solid state form of racemic tamsulosin free base are described in detail hereinafter.

In a first process ("Process A"), racemic tamsulosin free base may be prepared after first forming a racemic tamsulosin acid addition salt, such as tamsulosin hydrochloride, by reductive amination of the ketone of formula (4) by the amine of formula (5).

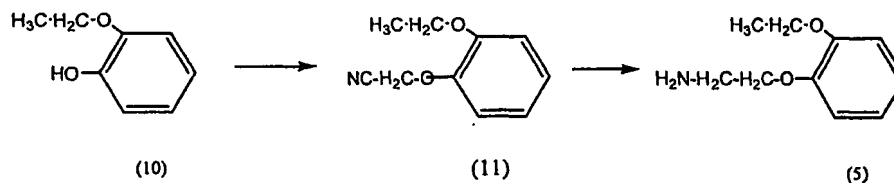


The (3-aminosulfonyl-4-methoxy)phenylacetone (4) is a novel compound and it may be prepared in analogy to a process described in US 5447958 for related compounds. The starting compound is 4-methoxyphenyl acetone which is chlorosulfonated by chlorosulfonic acid at 0-5°C. After treating the reaction mixture



with water, the resulting 3-chlorosulfonyl-4-methoxyphenylacetone (9) is formed in solid state and is isolated by filtration. The compound (9) is then treated in ethyl acetate solution with aqueous ammonia at 5°C. The formed crystals of crude (4) are recovered by filtration. The crude (4) may be purified by crystallization, e.g. from ethanol.

The 2-(o-ethoxyphenoxy)ethylamine (5) may be prepared according to a process described in BE 668124. In this process, 2-ethoxyphenol (10) reacts for 16-24 hours with chloroacetonitrile in refluxing acetone under presence of potassium carbonate. After filtration and evaporation of the solvent, the oily residue is dissolved in a suitable solvent such as ethanol or ether, treated with water and with a base such as ammonia or sodium hydroxide solution and crude o-ethoxyphenoxyacetonitrile (11) is obtained by evaporation of the solvent or by crystallization from the solvent. The crude (11) may be recrystallized from a suitable solvent, e.g. ethanol/water mixture. The compound (11) is catalytically hydrogenated under elevated pressure in a suitable solvent, e.g. toluene or toluene/triethylamine solution, using Raney cobalt or any other suitable catalyst. Crude free base of 2-(o-ethoxyphenoxy)ethylamine (5) is obtained after filtration and evaporation of the solvent as an oil.



It has now been discovered that the so obtained free base of (5) is contaminated by side-products and should be purified for the next step. However, normal alkaline extraction surprisingly resulted in too high of a loss. The amine (5) has unexpectedly high water solubility for an amine compound. It has been discovered that an effective way to purify the amine is to form a sulfonic acid salt of the amine, especially methane sulfonate or tosylate. The salt, particularly the methane

sulfonate salt of (5), may be isolated in solid, preferably crystalline state by conventional methods and may be used as an advantageous substrate in the next reaction step. The conversion of the free base of (5) into an acid addition salt and isolation of said salt in solid state enhances the purity of the compound (5), particularly it removes side products that resulted from hydrogenation such as 2-ethoxyphenol. The 2-(o-ethoxyphenoxy)ethylamine methane sulfonate thus forms a specific aspect of this invention.

The racemic tamsulosin is obtained by reductive aminolysis of the ketone (4) with the free base of amine (5) according to the process of US 4558156. If a salt of the amine (5) is used for the reaction, this salt is first converted to a free base by treatment with a suitable base, e.g. by sodium methoxide in methanol. An imino-compound is first prepared by contacting of both components in methanol. Hydrogenation catalyst such as platinum oxide or palladium/carbon is added to the reaction mixture and the mixture is hydrogenated by gaseous hydrogen, advantageously under enhanced pressure. After filtering off the catalyst, the reaction mixture is acidified with an acid, preferably with alcoholic or aqueous HCl, thereby forming an acid addition salt of racemic tamsulosin, preferably tamsulosin hydrochloride. The racemic tamsulosin salt is isolated in solid, preferably crystalline form by evaporation of the solvent or by crystallization from the solvent.

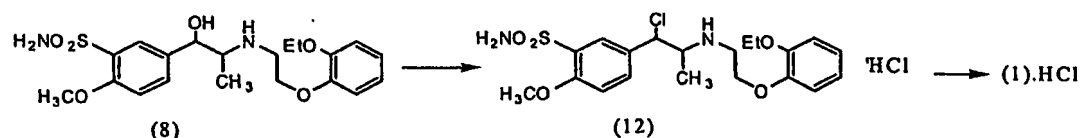
Tamsulosin free base in solid state is not obtained by the above Process A per se. It has been discovered that racemic tamsulosin free base may be obtained in solid state if a salt of tamsulosin, particularly tamsulosin hydrochloride, is treated with a

suitable base, such as alkali metal hydroxide, ammonia or organic amine, in a solvent system comprising water or water/lower alcohol mixture. The amount of base is preferably equimolar. The preferred solvent system is a mixture of water and methanol. The preferred base is sodium hydroxide. The preferred range of reaction temperature is from room temperature to reflux temperature. In this solvent system, tamsulosin free base precipitates in solid state from the solution at room temperature or at decreased temperature and is recovered by filtration. If desired, tamsulosin free base may be recrystallized from a suitable solvent.

The above process for obtaining tamsulosin free base in a solid state forms a specific aspect of the invention as it provides a tamsulosin substrate of high purity for resolution; i.e., dissolving in a solvent and subjecting to fractional crystallization with a chiral sulfonic acid.

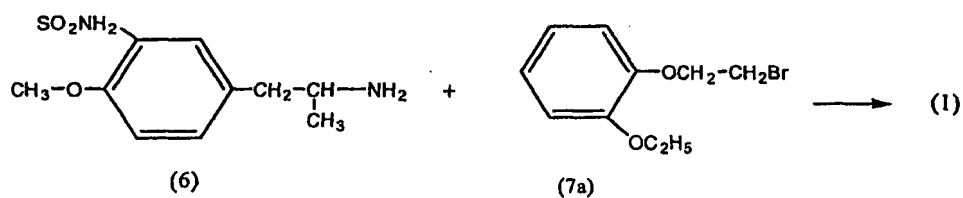
In a second process ("process B"), racemic tamsulosin hydrochloride may be prepared in a form of a hydrochloride salt from hydroxy-tamsulosin of formula (8) according to a method of EP 34432. Starting hydroxy-tamsulosin (8) may be prepared from the amine compound (5) according to US 4,217,305. The process comprises, in a first step, conversion of the hydrochloride salt of hydroxy-tamsulosin (8) into a chloro-tamsulosin hydrochloride (12) by means of reaction of (8) with thionylchloride in acetonitrile, and isolation of the product from the reaction mixture after its spontaneous crystallization from the reaction mixture. The compound (9) is subsequently dehalogenated by, e.g., catalytic hydrogenation using palladium on carbon as the catalyst at normal temperature and pressure. After concentration of the

reaction mixture, crystalline tamsulosin hydrochloride is obtained and it may be recrystallized from a mixture of methanol and ethanol.



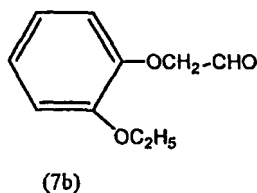
Tamsulosin free base is neither formed in said process nor does the analogous prior art manufacturing procedure allow for isolating it in solid state. To obtain tamsulosin free base in solid state, the above procedure of treating the tamsulosin salt with a base and precipitating the free base should be applied.

In a third process ("Process C"), racemic tamsulosin free base may be prepared directly by condensation of the racemic amine of the formula (6) with a bromo-compound of the formula (7a) in refluxing methanol. The conditions of the manufacturing procedure were disclosed in US 5447958, however, the starting amine (6) used therein was optically active. Tamsulosin free base (optically active) was obtained after separation of the reaction mixture by column chromatography in solid state and converted to hydrochloride. The column chromatography however makes this process impractical for industrial scale production.



However, it has been discovered that the process can be modified in such a way that a dipolar aprotic solvent such as dimethylformamide is used for the condensation of (6) with (7a) and the reaction temperature is between 70 and 100°C. After removal of the solvent by distillation under reduced pressure, hot water is added to the solid residue and tamsulosin free base is allowed to crystallize by decreasing the temperature. The obtained solid product may be further purified by extraction of the side products by hot water. Optionally, tamsulosin free base may be converted to tamsulosin hydrochloride by methods known per se and recovered back from the hydrochloride by a process given above. Starting reactants may be prepared by methods of prior art.

Alternately, the tamsulosin free base may be prepared from the racemic amine (6) by reductive amination of the aldehyde (7b); the manufacturing conditions including the synthesis of the starting aldehyde are described in AT 397960.



It should be noted that this Process C may also provide for a mixture of enantiomers of tamsulosin, if the starting amine (6) was provided as a mixture of enantiomers (e.g. by incomplete optical resolution) or if the reaction conditions caused some degree of racemization. Such tamsulosin product, as discussed above, is also a suitable substrate for the resolution process of the invention.

Optically pure or substantially pure (R)-tamsulosin, acid addition salts thereof and particularly (R)-tamsulosin hydrochloride prepared by the process of the invention are useful in the preparation of medicaments for treatment of various diseases or conditions including cardiac insufficiencies and benign prostatic hyperplasia among others. It may be used alone or in combination with other active components. Such medicaments may be formulated for peroral, transdermal or parenteral application, for instance in a form of tablets or capsules. The formulations comprise therapeutically effective amounts of the active substance together with a pharmaceutically acceptable carriers or diluents and may be prepared by any conventional method.

The present invention is more particularly described and explained by the following examples. It is to be understood, however, that the present invention is not limited to these examples and various changes and modifications may be made without departing from the scope of the present invention.

Example 1

Synthesis of racemic tamsulosin free base

a) Synthesis of 2-Methoxy-5-(2-oxopropyl)benzenesulfonamide (4)

Chlorosulfonic acid (426 g, 3.656 mol) is cooled down to -10 – (-15)°C. 4-methoxyphenylacetone (100 g, 0.609 mol) is added in such a rate as not to exceed temperature 5°C in reaction mixture. After addition of all amount of methoxyphenylacetone the reaction mixture is allowed to warm up to room temperature. Mixture is stirred for 2 hours at room temperature. The reaction mixture is then poured on stirred mixture of ice (1500 g) and water (1600 ml). Formed crystals are filtered, washed with cold water (200 ml).

The crystals are dissolved in ethylacetate (300 ml). Aqueous ammonia (600 ml) is cooled down to -5°C and the above ethylacetate solution is gradually added in such a rate as not to exceed 5°C. The mixture is then allowed to warm to room temperature and stirred overnight. Formed crystals are filtered, washed with water (200 ml) and ethanol (100 ml). Crystals of the crude product were recrystallized from ethanol to give 65 g of title compound.

b) Synthesis of (2-Ethoxyphenoxy)methyl cyanide (11)

Potassium carbonate (550 g, 3.98 mol) was added to acetone (1800 ml) and resulting suspension was stirred for 30 min. 2-Ethoxyphenol (460 g, 3.329 mol) was gradually added under stirring. The mixture was heated to reflux. Chloroacetonitrile (275 g, 3.642 mol) was added and the mixture was stirred under reflux for 24 hours. The reaction mixture was cooled down to room temperature. Solid was filtered off, washed with acetone (750 ml) and combined filtrates were evaporated to give oil. The oil was dissolved in ethanol (180 ml), the solution was

heated to reflux and mixture of water (530 ml) and aqueous ammonia (45 ml) was added. The mixture was cooled to 5 - 10°C under stirring. Crude crystalline product was filtered, washed with mixture of ethanol (250 ml) and water (400 ml). The crude product was recrystallised from ethanol /water mixture to give pure product (500 g).

**c) Synthesis of 2-(2-Ethoxyphenoxy)-1-ethanamine (5)
methanesulfonate**

(2-Ethoxyphenoxy)methyl cyanide (400 g, 2.257 mol) was dissolved in toluene (750 ml) and the solution was transferred to autoclave. 125 g of Raney cobalt was added to autoclave and the mixture was hydrogenated at 30-40°C and hydrogen pressure 1.7 to 1.2 Mpa for one hour. The catalyst was removed by filtration and the filtrate was evaporated to give an oil.

The oil was dissolved in ethylacetate (550 ml) and methanesulfonic acid (150 g) was added under stirring. The temperature was maintained between 20-25°C. Formed crystals were filtered, washed with ethylacetate (250 ml) and dried 40°C to give 430 g of the title product.

d) Synthesis of racemic tamsulosin hydrochloride :

2-(2-Ethoxyphenoxy)-1-ethanamine methanesulfonate (300 g, 1.08 mol) is dissolved in methanol (1 000 ml) at 40-50°C. Solution of sodium methoxide (30% soln, 195 g) is added under stirring. The mixture is cooled to 20-15°C. Formed sodium methanesulfonate is filtered off, and washed on filter with methanol (2 x 100

ml). Combined filtrates are transferred to autoclave. 2-Methoxy-5-(2-oxopropyl)benzenesulfonamide (263.3 g, 1.08 mol) is added and the suspension is stirred for 20 min. Catalyst Pt/C (5%Pt, 60 g) is added and the mixture is hydrogenated at 50-56°C and at hydrogen pressure 1.7 to 1.2 Mpa for 1.5 hour. The catalyst was removed by filtration and hydrochloric acid (37%, 90 g) was added to the filtrate under stirring. Formed crystals of tamsulosin hydrochloride were filtered, washed with methanol (500 ml) and dried at 50°C to give 360 g of title compound.

e) Synthesis of racemic tamsulosin free base

The crystals obtained in step d) were suspended in methanol (1 100 ml), the mixture was heated to reflux and sodium hydroxide solution (2M, 440 ml) was gradually added followed by water (350 ml). The mixture was cooled down to 10-15°C. Formed crystals were filtered and washed on filter with methanol (150 ml) and water (150 ml) mixture. Crystals were dried at 50°C to give 340 g of product.

Example 2A

Synthesis of racemic tamsulosin free base

5-(-2-aminopropyl)-2-methoxybenzenesulfonamide (200 g) was dissolved in dimethylformamide (950 ml) and 1-(2-Bromoethoxy)-2-ethoxybenzene (100.3 g) was added. The reaction mixture was heated to 80-85°C for 4 hours. Dimethylformamide was then distilled off under vacuum. Water (1000 ml) was added to solid residue and the mixture was heated to 80-90°C under stirring for 2 hours. The

mixture was cooled to room temperature. Formed crystals were filtered off and were suspended in water (900 ml). Suspension was heated to 80-90°C under stirring for 2 hours. Crystals were filtered, washed with water (200 ml) and dried to give tamsulosin base (150 g, 89.8%).

Example 2B

Purification of racemic tamsulosin free base

Tamsulosin free base (159 g) (purity 94%) was suspended in a methanol (280 ml)/ water mixture (280 ml). The mixture was heated to reflux until all material dissolved. Hydrochloric acid (37%, 44 g) was added and the mixture was gradually cooled down to 0°C. Formed crystals were filtered off, washed with cold methanol (70 ml). Wet crystals were suspended in methanol (450 ml) and the mixture was heated to reflux. Aqueous sodium hydroxide (2M, 150 ml) was then added. The mixture was cooled down and water (140 ml) was added. Formed crystals were filtered off, washed with methanol-water mixture (1:1, 100 ml) and dried. Yield 117 g of a crystalline product (70%, purity 99.7 %).

Example 3

Resolution of tamsulosin free base with (-) camphor-10-sulfonic acid

100 mg of racemic tamsulosin free base and 58 mg of (-)camphor-10-sulphonic acid were dissolved in 12 ml of ethanol while heating. The solution was

allowed to cool to room temperature and stored overnight. The formed solid was filtered off, washed with 1 ml of ethanol and 2 ml of ether and dried.

Optical purity (HPLC) : 61.3% of R-tamsulosin (-) camphor-10-sulfonate. After recrystallization from ethanol, the optical purity increased to 68.7%.

Example 4

Resolution of tamsulosin free base with (+)camphor-10-sulphonic acid

2.0 g of racemic tamsulosin free base and 1.71 g of (+)camphor-10-sulphonic acid was dissolved in 45 ml of methanol at reflux . The solution was slowly cooled up to 4C. The formed crystals were collected by filtration. Optical purity (HPLC) : 75% of (S)-tamsulosin-(+)camphor-10-sulphonate.

640 mg of the product were recrystallised from 5 ml of methanol. After standing overnight, the formed crystals were collected by filtration and dried. Optical purity (HPLC) : 94% of (S)-tamsulosin-(+)camphor-10-sulphonate.

300 mg of the product were recrystallised form 3 ml of methanol. After standing overnight at 30C, the formed crystals were collected by filtration, washed with ethanol and dried. Optical purity (HPLC): 96.5% of (S)-tamsulosin-(+)camphor-10-sulphonate.

Example 5

Resolution of racemic tamsulosin base by a process employing combination of (+)- and (-) camphor-10-sulfonic acids.

a)

1 200 g of racemic tamsulosin free base was suspended in 4700 ml of methanol and the mixture was heated to reflux. A solution of 682.4 g of (+)-camphor-10-sulfonic acid in 4700 ml of water was added to the mixture. Resulted mixture was heated to reflux and allowed to cool under stirring. At about 45°C, a solid started to precipitate. The mixture was cooled to 20-25°C and stirred at this temperature for 5 hours. Crystalline solid was filtered out, washed with 200 ml of cold (0°C) methanol and dried.

The solid product was suspended in 3050 ml of 50% aqueous methanol, heated to reflux and allowed to cool under stirring. After a solid began to precipitate (at approx. 55°C), the mixture was cooled to 20-25°C and stirred for 5 hours. The crystalline product was filtered out, washed with 150 ml of cold (0°C) methanol and dried. Yield: 693.4 g of (S)-tamsulosin (+) camphor-10-sulfonate.

b)

Mother liquors from both crystallizations were collected and 1020 ml of 2N aqueous solution of NaOH was added under stirring until the mixture was the slightly alkaline (pH 9-10). The resulting suspension of tamsulosin base was cooled to 0-5°C for 2 hours, filtered, washed with water and dried.

Yield: 697.5 g of tamsulosin free base comprising 76% of the (R)-enantiomer.

c)

The obtained tamsulosin free base was suspended in 1920ml of methanol and heated to reflux. A solution of 396.6 g of (-)-camphor-10sulfonic acid in 1920 ml of water was added to the boiling suspension. Reaction mixture was heated to reflux and allowed to cool under stirring. After a solid started to precipitate (approx. 35°C), the suspension was cooled to 20-25°C and stirred for 5 hours. Crystalline precipitate was filtered out, washed with cold methanol and dried. Yield : 806.8 g of tamsulosin (-)-camphor-10-sulfonate comprising 89.7% of the (R) enantiomer.

d) Recrystallisation of raw (R)-tamsulosin (-)-camphor-10-sulphonate

General procedure:

Raw (R)-tamsulosin (-)-camphor-10-sulphonate was dissolved under stirring in 3.5parts (by volume) of 50% aqueous methanol at reflux. The solution was allowed to cool until a solid began to separate and then cooled to 20-25°C. The mixture was stirred for 5 hours and the solid was separated by filtration. The solid was washed by 1.5 parts (by volume) of cold (0°C) methanol and dried. The crystallisation process was repeated several times with the following results :

Iteration	Yield (%)	Content (%)
0		89,7%
1	63,6%	95,7%
2	56,9%	98,4%

3	51,7%	99,5%
4	47,4%	99,8%

Example 6

Conversion of (R)-tamsulosin(-)camphor-10-sulfonate to (R)-tamsulosin free base

518,3 g of (R)-tamsulosin (-) camphor-10-sulfonate (opt. purity 99.8%) was dissolved under reflux in 3100ml of 50% aqueous methanol and 445 ml of 2N aqueous NaOH was added while hot. The resulted suspension was cooled to 0-5°C for 2 hours. The solid was filtered out, washed by water and dried. Yield : 315 g of (R)-(-)-tamsulosin free base containing 99,9% of R-isomer.

The product was dissolved under reflux in 3500 ml of 50% aqueous methanol and allowed to cool to 20-25°C under stirring. The suspension was stirred for 8 hours. The solid was filtered off, washed with 500ml of water and dried. Yield: 309.11 g (R)-(-)-tamsulosin free base comprising more than 99.9% of R-isomer.

Example 7

Conversion of (R)-tamsulosin free base into (R)-tamsulosin hydrochloride

309.11 g of (R)-(-)-tamsulosin free base was suspended in 1080 ml of 50%aqueous methanol, heated to reflux and treated with 125 ml of concentrated hydrochloric acid under stirring. The resulted solution was cooled, whereby a solid

crystallized. Resulted suspension was cooled to 0-5°C for 1.5 hours. Solid product was filtered off, washed with 500 ml of cold (0°C) methanol and dried. Yield: 320 g of (R)-(-)-tamsulosin hydrochloride comprising more than 99,9% of R-isomer.

Optical purity of tamsulosine base and salts, particularly the hydrochloride salt, was determined by HPLC on a chiral column. Measurement of optical rotation is less useful, as the measured values are sometimes quite low. For instance, a maximum found value of specific optical rotation $[\alpha]^{20}_D$ (c=0.35 in methanol) of (R)-tamsulosine hydrochloride of a high optical purity was about – 5.7 degrees

The invention having been thus described, it will be obvious to the worker skilled in the art that the same may be varied in many ways without departing from the spirit of the invention and all such modifications are included within the scope of the present invention as set forth in the following claims.

We Claim:

1. A process, which comprises:
 - (a) preferentially precipitating one diastereomeric sulfonate salt of tamsulosin from a solution containing a pair of diastereomeric sulfonate salts of tamsulosin to form diastereomeric enriched precipitate and diastereomeric enriched solute.
2. The process according to claim 1, wherein said pair of diastereomeric sulfonate salts of tamsulosin are tamsulosin camphor-10-sulfonates.
3. The process according to claim 2, wherein said pair of salts are (R and S)-tamsulosin-(+)-camphor-10-sulfonate or (R and S)-tamsulosin-(-)-camphor-10-sulfonate.
4. The process according to claim 1-3, wherein said precipitation occurs spontaneously after formation of said solution of diastereomeric pairs.
5. The process according to claim 1-3, wherein said precipitation is induced.
6. The process according to claim 1-3, wherein said solution contains more of one diastereomeric salt than the other.
7. The process according to claim 1-6, which further comprises forming said solution by dissolving a solid mixture of a pair of diastereomeric sulfonate salts of tamsulosin in a solvent.
8. The process according to claim 7, wherein said mixture contains more of one diastereomeric salt than the other.

9. The process according to claim 1-8, which further comprises dissolving a solid mixture of (R) and (S) tamsulosin free base in a solvent and reacting said free base with a chiral sulfonic acid to form said solution containing a pair of diastereomeric sulfonate salts of tamsulosin.
10. The process according to claim 9, wherein said tamsulosin free base contains more (R)-tamsulosin than (S)-tamsulosin.
11. The process according to claim 10, wherein said mixture contains (R)- and (S)-tamsulosin within the weight ratio of 75:25 to 95:5, respectively.
12. The process according to claim 1-11, wherein said solution contains a solvent selected from the group comprising an alcohol, water, or a mixture thereof.
13. The process according to claim 12, wherein said solvent is methanol and water.
14. The process according to claim 1-13, which further comprises:
 - (b) liberating tamsulosin free base from one of said diastereomeric enriched precipitate or solute to form optically enriched tamsulosin free base.
15. The process according to claim 14, which further comprises:
 - (c) reacting said optically enriched tamsulosin free base with a chiral sulfonic acid to form a pair of diastereomeric sulfonate salts of tamsulosin in a second solution and
 - (d) preferentially precipitating one of said pairs from said second solution to form a diastereomeric enriched second precipitate and a diastereomeric enriched second solute.

16. The process according to claim 15, wherein said diastereomeric pair of tamsulosin in step (a) is the same salt as the pair in step (d).
17. The process according to claim 15, wherein said diastereomeric pair of tamsulosin in step (a) is a different salt than said pair in step (d).
18. The process according to claim 17, wherein the difference in the salts is the optical rotation of the corresponding sulfonic acid.
19. The process according to claim 18, wherein one diastereomeric pair is (R and S)-tamsulosin-(+)-camphor-10-sulfonate and the other is (R and S)-tamsulosin-(-)-camphor-10-sulfonate.
20. The process according to claim 19, wherein the diastereomeric pair in step (a) is the (R and S)-tamsulosin-(+)-camphor-10-sulfonate and the diastereomeric pair in step (d) is the (R and S)-tamsulosin-(-)-camphor-10-sulfonate.
21. The process according to claim 20, wherein (S)-tamsulosin-(+)-camphor-10-sulfonate is precipitated in step (a) and (R)-tamsulosin-(-)-camphor-10-sulfonate is precipitated in step (d).
22. The process according to claim 15-21, wherein the said liberation step (b) is performed on said diastereomeric enriched solute.
23. The process according to claim 22, wherein the diastereomer containing the (S)-tamsulosin is preferentially precipitated in step (a) and the diastereomer containing the (R)-diastereomer is preferentially precipitated in step (d).
24. The process according to claim 15-23, which further comprises:

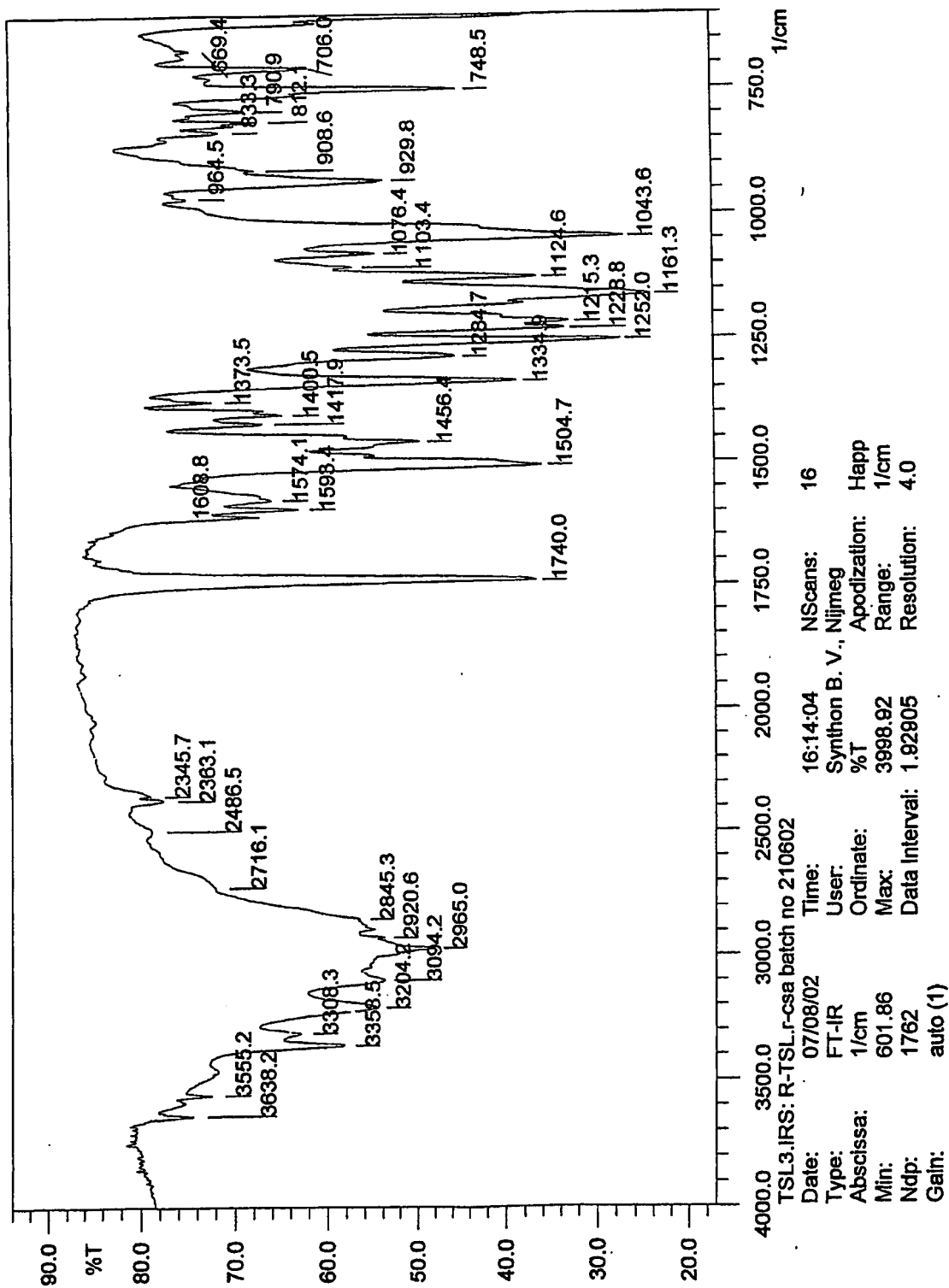
(e) liberating tamsulosin free base from one of said diastereomeric enriched second precipitate or second solute to form optically enriched tamsulosin free base.

25. The process according to claim 14-24, which further comprises re-precipitating said enriched precipitate from a re-precipitation solvent to form a further enriched precipitate and an enriched re-precipitation solute.
26. The process according to claim 25, wherein said liberation step (b) liberates the tamsulosin contained in said enriched solvent and said enriched re-precipitation solvent.
27. The process according to claim 14-26, wherein said optically enriched tamsulosin free base is converted to a pharmaceutically acceptable salt thereof.
28. The process according to claim 27, wherein said salt is enriched (R)-tamsulosin hydrochloride.
29. A method of separation of enantiomers of tamsulosin by fractional crystallization comprising using a chiral camphor sulfonic acid in said crystallization.
30. A compound selected from the group consisting of (R)-tamsulosin-(+)-camphor-10-sulfonate, (S)-tamsulosin-(+)-camphor-10-sulfonate, (R)-tamsulosin-(-)-camphor-10-sulfonate, and (S)-tamsulosin-(-)-camphor-10-sulfonate

31. (R)-tamsulosin(-)camphor-10-sulfonate having at least one of the following characteristics: IR spectrum shown in Fig. 1., melting range of 208-211°C or an optical rotation of about -17.2° ($c=0.5$ in methanol).
32. A composition comprising (R) and (S) tamsulosin or the salts thereof, wherein one of said (R) or (S) forms exceeds the amount of the other within the range of 60:40 to 95:5 parts by weight.
33. The composition according to claim 32, wherein one of said (R) or (S) forms exceeds the amount of the other within the range of 65:35 to 95:5 parts by weight.
34. The composition according to claim 33, wherein said (R) and (S) tamsulosin are both in the form of the free base.
35. The composition according to claim 33, wherein said (R) and (S) tamsulosin are both in the form of a salt.
36. The composition according to claim 35, wherein said salt is a camphor-10-sulphonic acid salt of tamsulosin.
37. The composition according to claim 32-36 wherein said composition is in a solid state, preferably a precipitate.
38. The composition according to claim 32-37, wherein the amount of (R) is greater than the amount of (S) in said composition.
39. The composition according to claim 38, wherein said amount of (R):(S) is within the range of 61:39 to 87:13 parts by weight.

40. The composition according to claim 39, wherein said amount of (R):(S) is within the range of 65:35 to 85:15 parts by weight.
41. The composition according to claim 40, wherein said amount of (R):(S) is within the range of 75:25 to 85:15 parts by weight.

1/1



INTERNATIONAL SEARCH REPORT

 Intern: application No
 PCT/NL 02/00657

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07C303/44 C07C311/39

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, COMPENDEX, INSPEC, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 447 958 A (NIIGATA KUNIHIRO ET AL) 5 September 1995 (1995-09-05)	32-34, 38-41
Y	examples 33(a) and (b) column 7, line 30 -column 8, line 2; claims 1,2	1-41
Y	JACQUES J ET AL: "ENANTIOMERS, RACEMATES, AND RESOLUTIONS, PASSAGE" ENANTIOMERS, RACEMATES, AND RESOLUTIONS, MALABAR, KRIEGER, US, 1991, pages 256,259-260, XP002027010 compound 34 in Table 2, page 256; page 259, paragraph 5.1.2 -page 260, paragraph 2	1-41

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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INTERNATIONAL SEARCH REPORT

Internat	Application No
PCT, IVL	02/00657

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